Enantioselective Synthesis of (−)-Pentazocine and (−)-Metazocine

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Abstract  We have accomplished an efficient asymmetric synthesis of (−)-pentazocine and (−)-metazocine from the readily available D-tyrosine, featuring a ring-closing metathesis (RCM) reaction for the formation of the C ring and an intramolecular Friedel–Crafts reaction for the assembly of the B ring. The new strategy established herein should be applicable to enantioselective synthesis of a broad range of chiral benzomorphans analogues, thereby facilitating the biological and medicinal chemistry studies of these clinically important molecules.

Key words  benzomorphans, pentazocine, metazocine, asymmetric synthesis, ring-closing metathesis reaction

Received: 22.10.2015  
Accepted after revision: 22.11.2015  
Published online: 05.01.2016  

Natural opium alkaloids such as (−)-morphine (1, Figure 1) and (−)-codeine (2) are two extremely important analgesics in spite of their addiction effect. Certain unnatural benzomorphans 3–6, accessed as morphine analogues by structural modification, have shown considerably reduced addiction effect while maintaining high potency and related pharmacokinetic properties. Pentazocine, a clinical drug, serves as an excellent example in this regard. Moreover, (−)-pentazocine is 20 times more potent than its (+)-enantiomer. However, few asymmetric synthetic routes are available for these molecules, which have been obtained in an enantiopure form by resolution of the corresponding racemic materials, chiral-auxiliary-induced asymmetric synthesis, or palladium-catalyzed asymmetric allylic alkylation.

Notably, amino acids have been widely used as inexpensive and readily available chiral starting materials in the asymmetric synthesis of natural and unnatural products. For example, we previously realized an efficient synthesis of (−)-9-epi-pentazocine, a diastereoisomer of (−)-pentazocine (3), from D-tyrosine and a formal synthesis of (+)- and (−)-aphanorphine from the same starting material, (2S,4R)-4-hydroxyproline. Herein, we wish to report a general and practical strategy for the rapid assembly of benzomorphans such as (−)-pentazocine (3) and (−)-metazocine (4).

The retrosynthetic analysis for (−)-pentazocine and (−)-metazocine is outlined in Scheme 1. We envisioned that the tricyclic framework of (−)-pentazocine (3) and (−)-metazocine (4) could be accessed stereoselectively via an intramolecular Friedel–Crafts reaction of alkene 7. The formation of 7 could be accomplished by a ring-closing metathesis (RCM) of diene 8, which could be derived conveniently from D-tyrosine. RCM has become one of the most powerful and broadly applicable synthetic tools for the synthetic organic chemists in constructing cyclic disubstituted or tetrasubstituted olefins which has been less investigated in a context of synthesis of complex natural and unnatural products.

As shown in Scheme 2, the assembly of (−)-pentazocine (3) commenced from known intermediate 9, available from D-tyrosine via five simple operations in excellent overall yield (87%). Mitsunobu alkylation (3-methyl-3-buten-1-ol, Ph3P, DIAD, 95%) followed by treatment with excess MeLi in THF afforded tertiary alcohol 11 in 72% yield. Regioselective dehydration was best accomplished with mesyl chloride along with disopropylethylamine in dichloromethane at
–20 °C,12 which gave terminal alkene 8 and its isomeric internal alkene 8′ in a combined yield of 74% (8/8′ = 10:1).13 Other reaction conditions (e.g., MeSO2Cl, Et3N; SOCl2, Et3N; SOCl2, DIPEA; SOCl2, pyridine) resulted in the formation of more of the undesired isomer 8′.

Next, RCM reaction of diene 8 was investigated. Both modified Hoveyda–Grubbs second-generation catalyst (15, Figure 2) and Grubbs second-generation catalyst (16) were tested in the catalytic cyclization of 8.14,15 Catalyst 15 has reportedly shown remarkable catalytic activity in the formation of cyclic tetrasubstituted olefins through a hindered RCM reaction. Surprisingly, it was ineffective for the cyclization of 8 when the standard conditions11h were adopted. A significant amount of the starting material remained intact even after prolonged heating at 60 °C, and there was little improvement after reloading more catalyst. Although the reaction was accelerated when the temperature was increased to 80 °C, the cyclization product was obtained in only 23% yield for a three-day reaction. Importantly, alkene 7 could be otherwise generated in 75% yield by treating 8 with 20 mol% of 15 (added in three portions) in refluxing benzene for three days. Meanwhile, it is worth noting that the yield considerably dropped to 59% if the total catalyst amount was decreased to 15 mol% (added also in three portions). To further optimize this reaction, we turned our attention to catalyst 16. This catalyst has been more widely used in organic synthesis and is less expensive than 15. To our delight, the yield of tetrasubstituted alkene 7 could be improved to 87% when the reaction was performed in the presence of 15 mol% of 16 (added in two portions) in toluene at 100 °C for 48 hours. In contrast, no cyclization took place when the reaction was conducted at any temperatures below 60 °C.

With alkene 7 in hand, the regio- and stereoselective intramolecular Friedel–Crafts reaction was set on the stage. Direct exposure of sulfonamide 7 to aqueous hydrobromic acid (48%) at reflux, by following the previously adopted protocol8,15 delivered no cyclization products at all, probably due to low solubility of the substrate in the aqueous medium, even at elevated temperatures. Alternatively, desulfonylation of 7 resulted in a secondary amine intermediary.
ate,16 which could not be transformed into the desired tricyclic structure in a straightforward manner, as subjecting this compound to hot hydrobromic acid led to decomposition of the material. Fortunately, tertiary amine 12, obtained from 7 via desulfonation and N-benzylation, smoothly underwent the desired intramolecular Friedel–Crafts cyclization in refluxing HBr to afford tricycle 13 in good yield (83%). Impressively, two new stereogenic centers were generated with excellent stereocontrol in this step, giving (−)-pentazocine (3) in 76% overall yield in two steps.17

Synthesis of (−)-metazocine (4) is described in Scheme 3. Again, desulfonylation of 7 and the subsequent reductive amination provided methylated amine 14.18 The (+)-enantio-mer of 14 was previously utilized by the Meyers’s group as a key intermediate in the synthesis of (+)-metazocine.5c Under essentially the same conditions adopted for compound 12 (Scheme 2), highly stereoselective intramolecular Friedel–Crafts reaction of 14 proceeded with concomitant O-demethylation to give (−)-metazocine in 74% yield.5,6

Scheme 3 Synthesis of (−)-metazocine (4)

In conclusion, we have developed an efficient and general strategy for the asymmetric synthesis of benzomorphanes [seven steps and 25% overall yield for (−)-metazo-

cine; nine steps and 24% overall yield for (−)-pentazocine) starting from D-tyrosine derivative 9. Key features of the current approach lie in an RCM reaction for the formation of the C ring containing a tetrasubstituted olefin as well as a highly regio- and stereoselective intramolecular Friedel–Crafts reaction for the assembly of the B ring. Moreover, the new strategy established herein should be applicable to enantioselective synthesis of a broad range of chiral benzomorphan analogues, thereby facilitating the biological and medicinal chemistry studies of these clinically important molecules.

Acknowledgment

Financial support was provided by the grants from National Basic Research Program of China (973 Program: 2010CB833200), NSFC (20625204; 20632030; 20772141; 90713007), and MOST (2009ZX09501-018).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561501.

References and Notes


L. Hu et al.


(13) The ratio was deduced by $^1$H NMR analysis.


(17) Synthesis of 3

To a solution of 13 (3.0 mg, 0.101 mmol) in EtOAc (1 mL), EtOH (1 mL), and 2.5 N HCl (0.25 mL) was added 10% Pd/C (10.1 mg, 10.1 mmol). The mixture was stirred under H$_2$ (1 atm) overnight (16 h) and filtered. The filtrate was concentrated to give a crude secondary amine as slurry, which was used for the next step without purification. The above crude secondary amine was dissolved in DMF (1.5 mL). NaHCO$_3$ (67.9 mg, 0.808 mmol) and prenyl bromide (30.1 mg, 0.202 mmol) were successively added. The mixture was stirred at r.t. for 2 h, diluted with H$_2$O (3 mL), and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated to give a residue, which was chromatographed (MeOH–CH$_2$Cl$_2$, 1:10) to afford (–)-pentazocine (22.0 mg, 76%) as a white solid: $[\alpha]_D^{20} = –135.3$ (c 0.44, CHCl$_3$). IR (film): $\nu = 3287, 2965, 2919, 2574, 1740, 1673, 1610, 1581, 1498, 1459, 1376, 1259, 1236, 1066, 934, 849, 807, 757$ cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.84$ (d, $J = 7.2$ Hz, 3 H), 1.20–1.39 (m, 1 H), 1.31 (s, 3 H), 1.66 (s, 3 H), 1.71 (s, 3 H), 1.90 (dt, $J = 12.8, 4.0$ Hz, 1 H), 1.95–2.06 (m, 1 H), 2.15 (dt, $J = 12.4, 2.4$ Hz, 1 H), 2.59–2.71 (m, 1 H), 2.71 (dd, $J = 18.8, 6.4$ Hz, 1 H), 2.93 (d, $J = 18.4$ Hz, 1 H), 3.04–3.13 (m, 1 H), 3.22 (d, $J = 6.4$ Hz, 2 H), 5.27–5.38 (m, 1 H), 6.63 (dd, $J = 8.0, 2.4$ Hz, 1 H), 6.71 (d, $J = 2.4$ Hz, 1 H), 6.94 (d, $J = 8.4$ Hz, 1 H), $^{13}$C NMR (75.47 MHz, CDCl$_3$): $\delta = 14.0, 18.1, 23.3, 25.2, 26.0, 36.2, 40.7, 41.2, 45.6, 52.2, 57.1, 112.5, 113.4, 120.1, 127.0, 128.1, 136.2, 142.8, 154.9. ESI-MS: $m/z = 286.1$ [M + H], 308.1 [M + Na]. HRMS (MALDI): $m/z$ calcd for C$_{19}$H$_{27}$NO + H: 286.2165; found: 286.2170.